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# Status of cardiovascular issues related to space flight: Implications for future research directions☆

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ABSTRACT

Compromised cardiovascular performance, occurrence of serious cardiac dysrhythmias, cardiac atrophy, orthostatic intolerance, reduced aerobic capacity, operational impacts of regular physical exercise, and space radiation are risks of space flight to the cardiovascular system identified in the 2007 NASA Human Integrated Research Program. An evidence-based approach to identify the research priorities needed to resolve those cardiovascular risks that could most likely compromise the successful completion of extended-duration space missions is presented. Based on data obtained from astronauts who have flown in space, there is no compelling experimental evidence to support significant occurrence of autonomic or vascular dysfunction, cardiac dysrhythmias, or manifestation of asymptomatic cardiovascular disease. The operational impact of prolonged daily exercise and space radiation needs to be defined. In contrast, data from the literature support the notion that the highest probability of occurrence and operational impact with space flight involving cardiovascular risks to astronaut health, safety and operational performance are reduced orthostatic tolerance and aerobic capacity, the resource cost of effective countermeasures, and the potential effects of space radiation. Future research should focus on these challenges.

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## 1. Introduction

A fundamental objective of the 2008 International Space Life Science Working Group (ISLSWG) meeting was to provide future direction for space research related to the cardiovascular system. In addition to a research emphasis placed on fundamental science by ISLSWG space agencies, the participants were specifically challenged to review the progress of the international community on space research to identify and prioritize the most important questions or problems needed to be resolved in order to assure the successful completion of extended-duration space flights such as missions to the Moon and Mars. This is particularly important in an environment of limited funding. The purpose of this paper is to provide a strategy that could be used to prioritize the direction of future space research for the cardiovascular system dictated by an evidenced-based approach.

## 2. Defining the 'most important' questions

Space life science research related to the identification of physiological adaptations potentially detrimental to human health and performance has been directed and funded by the National Aeronautics and Space Administration (NASA) as well as its international partners (e.g., The European Space Agencies (ESA) and national space agencies like DLR, CNES, ASI, Canada, and Japan). As such, the discussion outlined in this paper will focus on cardiovascular risks prioritized by NASA since these generally represent many of the concerns identified by most international space life science investigators.

As a support to the research focus on the well being of the astronauts exposed to extended space missions, the National Space Biomedical Research Institute (NSBRI) was established in 1996 under federal funding from NASA with the mission of conducting both ground-based and space research for the development of countermeasures against the deleterious effects of space flight on human health and performance. The overall strategic plan evolving from the NSBRI outlined specific critical risks of serious adverse health or performance consequences that would result from space flight and subsequently formed the basis for the initial NASA Bioastronautics Critical Path Roadmap (BCPR) first proposed in 2000. The priority for risks identified for the cardiovascular system included occurrence of serious cardiac dysrythmias, compromised cardiac function, manifestation of previously asymptomatic cardiovascular disease, and compromised cardiovascular response to orthostatic and exercise stress. The 2004 and 2005 revised versions of the BCPR identified diminished vascular function as an additional risk associated with space flight. In December 2007, NASA published their Human Integrated Research Plan that

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included the following prioritized list of risks associated with the cardiovascular system during space flight: (1) unnecessary operational limitations due to inaccurate assessment of cardiovascular performance; (2) cardiac rhythm problems; (3) orthostatic intolerance during re-exposure to gravity; (4) reduced physical performance capabilities due to reduced aerobic capacity; and (5) operational impact of prolonged daily required exercise. The strategy outlined in the remainder of this paper for identifying which of these risks should be considered as most critical for future research will be based on a critical review of the literature to determine whether there is evidence to support the notion that there is a high probability that these cardiovascular alterations occur and are, or may be, associated with having adverse health or operational impacts.

## 3. Operational limitations due to inaccurate assessment of cardiovascular performance

### 3.1. Evidence for cardiac atrophy and subsequent dysfunction

Evidence obtained from echocardiographic measurements taken on astronauts revealed a 19–28% lower stroke volume that was associated with a 15–23% reduction in cardiac size after space flight compared to preflight (Bungo et al., 1987; Convertino and Cooke, 2005). Subsequent magnetic resonance imaging measurements obtained from 4 astronauts who participated in the 10-d space mission revealed an average 12% reduction in left ventricular mass (Perhonen et al., 2001a), providing the first evidence of cardiac remodeling during space missions. Ground experiments that employed head-down tilt as a surrogate model of microgravity have provided evidence to support the space flight data that cardiac remodeling occurs with prolonged exposure of microgravity (Levine et al., 1997; Perhonen et al., 2001a,b; Spaak et al., 2005).

Despite the evidence that long-term space flight may lead to a reduction in myocardial mass, it is not clear whether such cardiac alterations pose a risk to myocardial function. For instance, regardless of any evidence for reduced stroke volume (Buckey et al., 1996; Bungo et al., 1987; Convertino, 1990; Convertino and Cooke, 2005; Levine et al., 2002) from flight or ground experiments conducted on humans, measures of myocardial function curves, ejection fractions, and arterial pulse wave velocities measured before, during and after space missions all suggest that there is no apparent impact of long duration exposure to microgravity on left ventricular systolic (contractile) function (Atkov et al., 1987; Convertino, 1990; Convertino and Cooke, 2005). With regard to cardiac filling, there is evidence that both reduced circulating blood volume and a stiffer heart (i.e., compromised diastolic function) probably contribute to the lower stroke volume reported upon return from space flight. However, the evidence from the literature indicates that cardiac remodeling and compromised diastolic function are not in themselves risk factors for space flight as much as the consequence of adaptation to microgravity, and may be eliminated by exercise.

### 3.2. Evidence for vascular dysfunction

Lower peripheral vascular resistance was measured in astronauts who displayed orthostatic intolerance during their stand test following space flight compared to astronauts who completed the test (Fritsch-Yelle et al., 1996a,b; Meck et al., 2004; Waters et al., 2002). This observation has been used to focus cardiovascular space research on a potential role of vascular dysfunction as a significant cardiovascular risk of space flight.

Although astronauts who are susceptible to orthostatic compromise after their return from a space mission display low vasoconstrictor responses, astronauts who display orthostatic stability after space flight exhibit elevated vascular resistance compared to preflight (Buckey et al., 1996; Fritsch-Yelle et al., 1996a,b; Levine et al., 2002; Meck et al., 2004; Waters et al., 2002). If exposure to microgravity in space flight caused a reduction in the vasoconstrictor response, one would expect an attenuated rise in vascular resistance in post-flight orthostatic tests in all astronauts. Against this expectation, maximal vascular resistance is not altered compared to preflight responses in astronauts who have reduced post-flight orthostatic tolerance and is significantly elevated in astronauts who are orthostatically stable after their return to Earth (Convertino and Cooke, 2005). These space flight results are consistently corroborated in ground experiments (Convertino et al., 1994; Convertino and Cooke, 2005; Kamiya et al., 2004). Taken together, these observations indicate that there is little evidence from human space flight to support the notion that vascular responsiveness is an important factor associated with cardiovascular risk. Instead, a reduction in vasoconstrictor reserve has emerged as a mechanism that contributes to orthostatic intolerance (Convertino and Cooke, 2005; Engelke et al., 1996; Fu et al., 2004) and may provide an alternative explanation for the discrepancy in vascular function between orthostatically tolerant and intolerant astronauts after space flight.

### 3.3. Evidence for manifestation of previously asymptomatic cardiovascular disease

There are no clinical observational reports or published data to support the basis for directing research toward the exacerbation of previously undetected cardiovascular disease (e.g., coronary artery disease) as a major cardiovascular risk factor for long duration space flight. Although the absence of evidence cannot be justification for dismissing a potentially important research direction, regularly scheduled and thorough physical examination conducted by flight surgeons on astronauts before and after space flight have failed to identify any evidence (published documentation) to suggest that conditions of space flight *per se* might cause a pre-existing cardiovascular disease to become symptomatic or to accelerate the progression of the disease. This may simply be the result of highly effective selection of very healthy people within the astronaut corps, which is a process that should continue (Hamilton et al., 2005).

## 4. Cardiac rhythm problems

Among a number of discussions and anecdotal reports, the publication of a case study describing a single isolated non-sustained, asymptomatic 14-beat ventricular tachycardia episode in an astronaut during an extended space mission (Fritsch-Yelle et al., 1998) focused concern on the possibility that long duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. However, electrocardiogram (ECG) tracings examined on astronauts during or following their space missions while performing their routine tasks (D'Anno et al., 2003; Fritsch-Yelle et al., 1996a; Goldberger et al., 1994) or while performing extravehicular activities (Rossum et al., 1997) revealed no greater incidence of cardiac dysrhythmias. Extensive databases designed to examine ECG tracings obtained from astronauts exposed to long duration space missions have revealed "no pathology in the myocardial bioelectrical activity" (Golubchikova et al., 2003). Even the reported ventricular tachycardia episode during a space mission (Fritsch-Yelle et al., 1998) was described as a probable normal variant (Ellestad, 1998). Indeed, less serious cardiac dysrythmias are common events that can be initiated by factors not related specifically to space flight such as transient myocardial inflammation, electrolyte shifts, heat, pollutants, and anxiety. Although the use of new analytical techniques cannot be dismissed as an approach to better identify aberrant electrical activity during a space mission, the current published data provide little evidence to justify a high research priority on the study of serious cardiac dysrhythmias as a major cardiovascular risk factor associated with space flight.

## 5. Impaired cardiovascular response to orthostatic stress

Orthostatic hypotension and compromise following return from space flight has been well documented since early NASA space missions, and pre-syncopal symptoms have been reported in 28–65% of mission specialists or scientists studied during stand or tilt tests after returning from specific life science space missions (Buckey et al., 1996; Fritsch-Yelle et al., 1996b; Meck et al., 2004; Waters et al., 2002). It is clear that the inability of an astronaut to stand and perform an emergency egress from a spacecraft after landing could result in a life-threatening event, and consequently, may represent one of the highest risks to the safety, well-being, and performance of astronauts. Clearly, there is strong evidence that orthostatic compromise is a high priority for cardiovascular research efforts.

## 6. Reduced aerobic capacity and physical performance capabilities

The most definitive study in which actual aerobic capacity was measured before and after space flight demonstrated that there may be as much as a 20–25% reduction in maximal oxygen uptake associated with exposure to microgravity (Levine et al., 1996). However, little research has focused on defining how reduced aerobic capacity translates to physical performance during the mission and upon return to Earth. Perhaps more important is the evidence obtained from both in-flight and ground experiments indicating that regular intense exercise during the mission can protect cardiovascular functions associated with maintaining physical work capacity. Thus, not only should space research of the cardiovascular system focus on exercise countermeasures, but the operational impact of prolonged daily exercise regimens has evolved as a cardiovascular 'risk' outlined in NASA's Human Integrated Research Plan.

## 7. Operational impact of prolonged daily exercise

The use of physical exercise countermeasures for protection against deleterious effects of space flight on cardiovascular function involves consideration of load intensity, duration and frequency. Work rates and metabolic costs of in-flight exercise reported in the literature indicate aerobic exercise regimens of long duration and moderate intensity (Convertino, 1990). The resulting daily exercise can be extremely costly to the operational workday and life support resources. Table 1 outlines the average estimated daily expenditures of energy, oxygen and water required to support exercise regimens during early Russian space missions. If the combination of exercise intensity, duration and frequency could be optimized to reduce the total exercise volume in half, an additional 1–2 weeks of food, oxygen and water could be saved with more time to perform operational tasks. It is clear from these data that an important research direction for cardiovascular risks is to identify the most effective and efficient exercise countermeasures for minimal operational impact.

**Table 1**
Average estimated daily expenditures of energy (food), oxygen, and water during baseline activities and physical exercise. Additional days of space-flight support represent the amount of added resources if exercise were not performed over a 6-month period. Estimates taken from Convertino, 1990.

| | Energy, kcal/day | Oxygen, L/day | Water loss (sweat), L/day |
|---|---|---|---|
| Exercise | 725 | 75 | 0.9 |
| 24-h total | 3150 | 500 | 2.7 |
| Additional days of support | 21 | 14 | 30 |

## 8. Cardiovascular effects from space radiation

Although the emphasis of research into the health effects of space radiation has been focused on cancer, there is an emerging hypothesis that vascular inflammation could result from chronic, low-level radiation exposure and consequently represent a risk factor for atherosclerosis. Such a notion is consistent with increased risk of cardiovascular disease reported among radiation-therapy patients, atomic bomb survivors, and radiation technicians. As such, the NSBRI Cardiovascular Research Team has focused a portion of its program on assessing the potential cardiovascular risks associated with space radiation.

## 9. Summary

With limited funding availability, the prioritization of space life science research questions on the cardiovascular risks associated with space flight should be dictated by scientific evidence and operational impacts. The assessment of data by this approach is outlined in Table 2. Although operational impact may be considered high, critical review of data obtained from space flight and ground experiments indicates that the probability for occurrence of serious cardiac dysrhythmias, previously asymptomatic cardiovascular disease, or compromised cardiac systolic and vascular function is substantially low enough, particularly in the presence of exercise countermeasures, that less priority should be placed on these research directions. In contrast, the scientific evidence supports the notion that the highest probability of occurrence and operational impact with space flight involving cardiovascular risks to astronaut health, safety and operational performance are reduced orthostatic tolerance and aerobic capacity, the resource cost of effective countermeasures, and the potential effects of space radiation.

Although one may not agree with the specific interpretations of results and priorities presented in this review, it is important that an evidence-based approach of identifying and justifying the most important questions be adopted. As such, the following recommendations are made. First, it is important to identify and focus research efforts on the most important cardiovascular issues rather than attempt to cover all issues. Second, it is paramount to focus future directions of space research on the cardiovascular system on those risks that have a high probability for occurrence and high

**Table 2**
Qualitative assessments of the probability of occurrence and operational impact of the cardiovascular risk factors identified in the NASA Human Integrated Research Plan. Assessments are based on the author's interpretation of data extracted from published results of space research.

| Cardiovascular risks | Probability of occurrence | Operational impact |
|---|---|---|
| Incidence of cardiac dysrhythmia | Low | ? |
| Exacerbation of cardiac disease | Low | High |
| Autonomic/vascular dysfunction | Low | Moderate |
| Orthostatic tolerance | High | Moderate |
| Reduced aerobic capacity | High | Moderate |
| Impact of prolonged daily exercise | High | High |
| Radiation effects | ? | High |

operational impact. Finally, the need for incorporating basic science as a supporting component to operational impact will be necessary in the development of effective countermeasures.

## 10. Department of defense disclaimer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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